

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

Remarks

In the Office Action, the Examiner noted that claims 1, 2, 4-15, 18-26, 28, 29 and 31-35 are pending in the application; and that claims 1, 2, 4-15, 18-26, 28, 29 and 31-35 are finally rejected. By this amendment, claims 1, 10, 15 and 26 have been amended. Thus, claims 1, 2, 4-15, 18-26, 28, 29 and 31-35 are pending in the application. No new subject matter has been inserted through these amendments. All of the amendments are fully supported by the specification and are discussed further in detail below.

Claim 1 is amended to obviate the outstanding rejections and to place the application in condition for an allowance. In the alternative, the amendments made are believed to reduce the number of outstanding issues so as to place the application in better form for appeal. For this purpose, a notice of appeal is also enclosed herewith. Claims 10, 15 and 26 are amended to correct certain obvious typographical errors. Specifically, in claims 15 and 26 the compound name appeared as "N-m.tolyl" which is amended to correctly read as "N-m-tolyl." Similarly, claim 10 was amended to correct the typographical error of the word "unsubstituted." The Examiner's rejections are respectfully traversed below.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-2, 4-15, 18-26, 28-29 and 31-35 stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner alleges that the "specification, while being enabling for "thiol" and "hydroxy" or amino radical as substituents in the triazine, does not reasonably provide enablement for thio radical substituted with halogen, oxy radical substituted with halogen or amino radical substituted with halogen as recited for compound of claim 1." Further, the Examiner alleges that claims 2, 4-15, 18-26, 28-29 and 31-35 are also rejected as they depend upon the rejected base claim under 35 U.S.C. § 112, first paragraph.

Applicants respectfully submit that claim 1, as amended, clearly obviates this rejection because of the fact that such halogen substituted thio, oxy and amino radicals have been deleted from claim 1. Accordingly, it is respectfully submitted that this

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

rejection is rendered moot, and therefore, rejection as to claims 1-2, 4-15, 18-26, 28-29 and 31-35 be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-2, 4-9, 11-15, 18-26, 28-29, 31 and 34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Daeyaert et al (US 6,150,360).

Contrary to the views of the Examiner Applicants respectfully submit that claims 1-2, 4-9, 11-15, 18-26, 28-29, 31 and 34 are patentably distinguishable over Daeyaert et al for all of the arguments advanced by the Applicants in their previous response of November 14, 2003 and further in view of the new arguments presented below.

In particular, Daeyaert et al. discloses a series of trisubstituted 1,3,5-triazine derivatives. More particularly, Daeyaert teaches phenyl and 2-pyridinyl-amino triazine derivatives. However, compounds of the present invention are much different from those of Daeyaert in that it only includes 4-pyridinyl amino derivatives of triazine compounds among various other compounds and with various other substituents on the triazine ring. Because of this the Examiner has maintained that the compounds of the present invention are "equivalent" to the compounds of Daeyaert with which we respectfully disagree.

Specifically, independent claim 1, as amended, recites a compound which binds G-quadruplex structure of a telomere comprising a nitrogen containing aromatic ring-NR₃-distribution agent-NR'₃-nonaromatic hydrocarbon chain. More specifically, claim 1 recites that the nitrogen containing aromatic ring may be a quinoline optionally substituted with N(Ra)(Rb), a quinoline in its quaternary form, a benzamidine or a pyridine attached at the 4-position. None of these features is either taught or suggested by Daeyaert et al. Even more importantly as we asserted in our previous response Daeyaert does not even remotely suggest the compounds of the present invention so as to motivate one of skilled in the art to arrive at the present invention at the time Applicants made this invention. Naturally, the benefits offered by the present invention can never be obtained by the teachings of Daeyaert et al., contrary to the views of the Examiner. Thus, it is

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

respectfully submitted that claim 1 is not obvious over Daeyaert et al, and therefore, satisfies the requirements of 35 U.S.C. § 103(a).

The dependent claims 2, 4-9, 11-15 and 34 depend directly or indirectly upon claim 1 and further recite certain limitations, and therefore, dependent claims 2, 4-9, 11-15, 18-26, 28-29, 31 and 34 are also patentably distinguishable over Daeyaert et al. Thus, it is respectfully submitted that rejection as to claims 2, 4-9 and 11-15 should also be withdrawn. For instance, dependent claim 2 limits the distribution agent to be triazine or diazine. Dependent claims 4-7 recite preferred embodiments of the non-aromatic hydrocarbon chain. Dependent claims 8-15 recite a preferred triazine compound of the invention. Dependent claim 34 recites a pharmaceutical composition comprising a compound of claim 1. Again, none of these features is neither taught nor suggested by Daeyaert. Further, it is submitted that there is no motivational teachings in Daeyaert such that one of ordinary skill in the art could arrive at the instant invention. Thus, it is respectfully submitted that rejection as to claims 2, 4-9 and 11-15 be withdrawn.

Similarly, independent claim 18 recites a specific tri-substituted triazine compound having certain preferred substituents. As acknowledged by the Examiner no such compound is taught or suggested by Daeyaert. Dependent claims 19-26, 28-29 and 31 depend directly or indirectly upon independent claim 18 and further recite additional limitations. None of these features is again taught or suggested by Daeyaert et al or there is no motivational teaching for one of skilled in the art of medicinal chemistry to arrive at the present invention. Accordingly, withdrawal of rejection as to claims 18-26, 28-29 and 31 is respectfully requested.

However, the Examiner has maintained that Daeyaert et al. teaches generically certain compounds of the instant invention. More specifically, the Examiner alleges that Daeyaert teaches triazine compounds which correspond to instant triazine with pyridine as nitrogen containing aromatic ring and L as nonaromatic hydrocarbon chain groups. Further, the Examiner directs the Applicants to Daeyaert for compounds made, Table 2 and Table 3. However, what Examiner does not point out is that Daeyaert et al. have not made even a single pyridine containing compound. Instead, all of the compounds listed

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

therein are cyanophenyl derivatives; see Table 2 and Table 3. Even more importantly, Daeyaert et al., although non-enabling, generically disclose only the pyridine compounds substituted at the 2-position. However, in the instant invention claim 18 already recited preferred pyridine compounds to be attached at 4-position. Claim 1, as amended, also includes only the pyridine compounds attached at the 4-position. Therefore, as acknowledged by the Examiner, the instant claims are much different from the Daeyaert. The present invention claims various compounds which not only includes pyridine compounds attached specifically at the 4-position but also includes quinoline, quinolinium and benzamidine compounds, among many other compounds. Thus, the compounds of the present invention must be considered much different from those of Daeyaert et al.

In spite of this, Examiner concludes that there is "equivalency" teaching in Daeyaert et al by drawing attention to col. 9 and Table 2 and Table 3. As Applicants pointed out above, in direct contradiction to Examiner's conclusion, Daeyaert has not provided any specific example of the pyridine compound other than generically claiming pyridine compounds attached at the 2-position. Nevertheless, Applicants respectfully submit the Examiner's "equivalency" argument is quite flawed especially in view of the fact that this is a complicated art. To illustrate this in a simple way, Applicants direct the Examiner's attention to two simple well known compounds water and hydrogen sulfide wherein they are different only by the substitution of oxygen for sulfur. But their physical attributes are tremendously different even though a non-artisan may not appreciate such difference.

Now, reverting to the instant issue at hand, Applicants submit that the art of medicinal chemistry is much more complex and it is extremely difficult to say merely from some prior art reference that the invention at issue is obvious simply because there is some remote level of "equivalency" teaching in the prior art. It is often difficult to predict activity of the same functional group in different environment let alone at different positions as currently taught by the instant invention. That is, 4-substituted pyridine compounds of the present invention are much different from the 2-substituted

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

pyridine compounds of Daeyaert et al. As stated in a leading text book of organic chemistry:

".....it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is part of. The reaction at the functional group is influenced by the rest of the molecule. This influence *may be great enough to stop the reaction completely* or to make it *take an entirely unexpected course*. Even when *two compounds with the same functional group undergo the same reaction*, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. *The greatest variations may be expected when additional functional groups are present.*¹" (emphasis added)

From this it can additionally be concluded that a skilled artisan is not motivated by the teachings of Daeyaert et al to arrive at the instant invention. Even more importantly, the Board has held that in an obviousness determination the prior art must provide some impetus for the one of ordinary skill in the art to arrive at the present invention. As stated by the Board:

At best, the Examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. *This is an inappropriate standard for obviousness....That which is within the capabilities of one skilled in the art is not synonymous with obviousness....That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus*

¹ Advanced Organic Chemistry, Chapter 9, "Effects of Structure on Reactivity", p 363, J. March, 5th Ed., John Wiley & Sons, 2001.

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

to have led one of ordinary skill in the art to combine the teachings of the references to make the claimed invention² (emphasis added).

From the foregoing discussions it is clear that there is neither logic nor sound scientific reasoning that provides sufficient impetus for one of ordinary skill in the art to arrive at the present invention merely following the prior art reference. That is, Daeyaert et al. barely disclose a 2-pyridine substituted triazine compound with no specific example of such a compound. This is undoubtedly insufficient to motivate a skilled artisan to arrive at the instant invention which not only teaches triazine substituted with pyridine (at 4-position) but also various other triazine compounds including quinoline and quinolinium substituted compounds as an antitelomerase agent. Thus, it is submitted that Examiner erred in concluding "equivalency" and that there was enough motivation to arrive at the present invention following the teachings of Daeyaert et al.

Further, in an obviousness analysis, the Board of Patent Appeals and Interferences ("Board") as well as the Court of Appeals for the Federal Circuit (CAFC) have provided guidance to determine whether or not the invention under examination is rendered obvious in view of the cited art. First, there must be logical reasoning which provides sufficient impetus for one of ordinary skill in the art to arrive at the claimed invention based on the prior art at the time the invention was made. As stated by the Board:

"..... fact that invention's theoretical mechanism can be reconstructed and explained by means of logic and sound scientific reasoning does not, however, support obviousness determination *unless that logic and reasoning would supply sufficient impetus to have led one of ordinary skill in art to combine references to make claimed invention*, and thus examiner cannot establish obviousness by locating references which describe

² Ex parte Levengood, 28 USPQ2d 1301-02 (Bd. Pat. App. & Inter. 1993); a somewhat similar result was reached by the court in *In re Brouwer* holding that the claim under examination may not be rejected under

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

various aspects of applicant's invention unless examiner also provides evidence of motivating force which would impel person skilled in art to do what applicant has done³. (emphasis added)

Applying these criteria to the present situation, it is respectfully submitted that the Examiner has not provided any evidence of motivating force such that a person skilled in the art would have done what Applicants have taught in the instant invention. That is, Applicants have specifically disclosed and claim discrete structures of various telomere binding compounds including quinoline and/or pyridine substituted triazine compounds. As noted above, Daeyaert et al. have not shown any structures of these types. Thus, we submit that there is no logic or sound scientific reasoning such that one of ordinary skill in the art would arrive at the instant invention based on the teachings of Daeyaert et al.

Additionally, the courts have also looked for reasonable expectation of success in arriving at the claimed invention based on the cited prior art. As noted by the Federal Circuit:

"Rejection of claimed subject matter as obvious under 35 USC 103 in view of combination of prior art references requires consideration of whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that such person would have reasonable expectation of success; *both suggestion and reasonable expectation of success must be founded in prior art, not in applicant's disclosure*⁴". (emphasis added)

35 U.S.C. § 103 unless the prior art suggested the desirability of such a modification as claimed: see *In re Brouwer*, 77 F.3d 422, 37 USPQ 2d 1663 (Fed. Cir. 1996).

³ *Ex parte Levengood* (Bd. Pat. App. & Int.) 28 USPQ2d 1300 (1993)

⁴ *In re Vaeck* (CA FC) 20 USPQ2d 1438 (1991)

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

Again, from the foregoing description of Daeyaert et al., it does not suggest with any degree of certainty success in arriving at the present invention. In fact, as we argued above, Daeyaert et al. does not even remotely suggest the present invention.

From the foregoing discussion of technical treatise and case laws, Applicants reiterate that Examiner's conclusion of "equivalency" is totally flawed and submit that the Examiner has used improper analysis for determining the *prima facie* obviousness, which we further discuss in greater detail below. For now, Applicants would like to reiterate that the Examiner's conclusion can at best be characterized as "obvious to try," as we noted in our previous response. Again, courts have consistently held that this is not the standard of 35 U.S.C. § 103(a)⁵. As stated by C.C.P.A.⁶:

".....application of the "obvious to try" test would often deny patent protection to inventions growing out of well-planned research which is, of course, guided into those areas in which success is deemed most likely. These are, perhaps, the obvious areas to try. But resulting inventions are not necessarily obvious. *Serendipity is not a prerequisite to patentability.....*" (emphasis provided by Applicants)

In direct support of C.C.P.A.'s opinion and many of the case laws cited as herein (see footnotes 5 and 6), Applicants draw Examiner's attention to Table 2, Table 3 and Table 4 of Daeyaert et al. As summarized therein the melting points and biological properties of various compounds are vastly different even though as contended by the Examiner they are supposedly "equivalent." In addition, it is important to note that all of the compounds listed therein are cyanophenyl derivatives and none are the 2-pyridine

⁵ *In re Geiger*, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987) ("At best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. § 103.")

⁶ *In re Lindell*, 155 USPQ 521, 523 (C.C.P.A. 1967); a somewhat similar opinion was held by the Board in a recent case "*Examiner's rejection of claims..... reflects "obvious to try" approach of "armchair" chemist, and must be reversed.*" See *Ex Parte Maizel*, 27 USPQ 2d 1662 (B.P.A. & I. 1992).

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

compounds, the compounds at dispute here, again in direct contradiction to examiner's contention. With this, it can very readily be concluded that the one of ordinary skill in the art of medicinal chemistry would readily appreciate that this art is an "unpredictable art." More importantly, it is almost impossible to predict how one compound would function vs. another compound. On the other hand, Applicants have now presented a well thought out series of compounds, see Example 1 and Example 2 of the specification. Thus, Applicants respectfully submit that the present invention satisfies the requirement of 35 U.S.C. § 103(a). In addition, the Federal Circuit has stated the following consideration when determining whether a claimed compound would have been obvious:

"Normally a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. Similarly, a known compound may suggest the analogs or isomers, either geometric isomers (*cis v. trans*) or position isomers (e.g., *ortho v. para*)."⁷

The court has emphasized that when the prior art teaches a specific, structurally definable compound, the issue is whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. *This is what Applicants have repeatedly argued in their previous response that there is no suggestion let alone motivational teachings for one of ordinary skill in the art to arrive at the present invention.* A couple of analogous cases involving similar problem as in the present case are worth mentioning here. In *In re Grabiak*⁸, the court held that

⁷ *In re Deuel*, 51 F.3d 1552, 34 USPQ 2d 1210, 1214 (Fed. Cir. 1995)

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

"[In] the case before us there must be adequate support in the prior art for the [prior art] ester/[claimed] thioester change in structure, in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant."

A similar result was reached in *In re Lulu*⁹:

"The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."

In summary, it is evident from the foregoing discussions that the compounds of the present invention are structurally different from any of the compounds of Daeyaert et al. It is also evident that there is no motivational basis for one of ordinary skill in the art to arrive at the present invention following the teachings of Daeyaert et al.

For the extensive reasons advanced above, Applicants respectfully but forcefully contend that claims 1-2, 4-9, 11-15, 18-26, 28-29, 31 and 34 are patentable. Therefore, reversal of rejections under 35 U.S.C. § 103(a) is courteously solicited.

Conclusions

In view of the above Remarks, it is respectfully submitted that claims 1, 2, 4-15, 18-26, 28, 29 and 31-35 are now in condition for allowance and the early issuance of this case is respectfully requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

As noted above, Applicants are submitting concurrently herewith a petition requesting two-month of extension to make this Rule 116 Response/Amendment timely. Also enclosed herewith is a Notice of Appeal. The commissioner is hereby authorized to

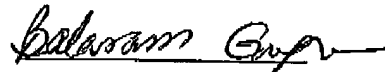
⁹ *In re Grabiak*, 769 F.2d 729, 731-32, 226 USPQ 70, 872 (Fed. Cir. 1985)

Application Ser. No.: 10/040,370
Filing Date: January 09, 2002
Examiner: Venkataraman Balasubramanian

charge fees due to these papers, and any other fees that are deemed necessary for this submission to Deposit Account No. 18-1982 for Aventis Pharmaceuticals Inc. Bridgewater, NJ. Please credit any overpayment to Deposit Account No. 18-1982.

Respectfully submitted,

July 12, 2004



Balaram Gupta
Registration No. 40,009
Attorney for Applicants

Aventis Pharmaceuticals Inc.
Patent Department
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3364
Telefax: 908-231-2626

⁹ *In re Lahu*, 747 F.2d 703, 705 223 USPQ 1257, 1258 (Fed. Cir. 1984).